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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,631	09/21/2001	Ronald Martin Burch	6750-018	6957

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,631	BURCH ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *2,3,6,12,13,16,23,24 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7-11,14,15,17-22,25,26 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/9/02; 12/20/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's species election of gondadotropin releasing hormone in the response filed October 30, 2003 is acknowledged.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

For example: on page 3 line 32 the patent number is not complete.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, submitted on January 9, 2002 and December 20, 2002, are attached to the instant Office Action.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information

submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by applicant on form 1449 or by the examiner on form PTO-892, they have not been considered.

The incorporation of essential material in the specification by reference to a patent, or to a publication is improper. In this instance Applicant's are incorporating a co-pending application, neither the application number not the patent number is not listed in the specification, see page 8, lines 35-36. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

MPEP 608.01(p) states that in any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. or application which itself incorporates "essential material" by reference, or (4) a foreign application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 7-11, 14, 15, 17-21, 22, 25, 26 and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation "having at least one CDR that has a portion of an antigen of a cell or protein involved in reproduction function" is unclear. Does the CDR actually contain sequences from antigens of a cell or proteins involved in reproduction function? Or does the CDR merely bind to antigens of a cell or proteins involved in reproduction function? It is not clear what is encompassed by the calims.

The limitation "said one or more amino acid substitutions of one or more amino acid residues that do not have a sulfhydryl group at one or more positions corresponding to one or more cysteine residues that form a disulfide bond in said second immunoglobulin" is not clear from the claim whether any substitution that does not involve a sulfhydral group (cysteine or methionine) is contemplated by the limitation. The way the claim is presented the substitutions involve residues that do not have a sulfhydral group. Or is the limitation to be the insertion of an amino acid that does not form disulfide bonds at a position that normally contains a cysteine residue. Because the claims are not clear in limiting the number of substitutions and in indicating that the substitutions must include the cysteine residues involved in the intrachain disulfide bonding, the claims can be interpreted to include compositions comprising polyclonal

antibodies which would meet the limitation of having one or more (i.e. an unlimited number of) amino acid substations. Clarification of what is contemplated by the invention is required.

The term "identical" in conjunction with an unlimited number of amino acid substitutions makes the term "identical" indefinite. It is not clear at point/number of amino acid substitutions the two compounds will cease being "identical".

For purposes of the instant Office action the claims have been interpreted to be a composition comprising two (or more) antibodies (see figure 5), the antibodies react with the gonadotrophin releasing hormone, because of their reactivity they are interpreted as being "identical". The two (or more) antibodies may differ by an unlimited number of amino acid substitutions.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5, 7-11, 14, 15, 17-21, 22, 25, 26 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition regarding an antigen from a molecule involved in reproduction, does not reasonably provide enablement for "a vaccine". The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The term "vaccine" implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined in the prior art as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease.

In this instance the antigenic proteins involved in reproduction cannot be fairly described as being involved in a disease process or as leading to a disease. Therefore, the claimed composition comprising two antibodies would not fall within the meaning of the term vaccine as the antibodies are not directed to killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Claiming the composition comprising two antibodies would obviate the instant rejection.

Claims 1, 4, 5, 7-11, 14, 15, 17-21, 22, 25, 26 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a genus of compounds defined only by their function "sufficient to induce an anti-idiotype response" wherein the relationship between the structural features of members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest as being "sufficient to induce an anti-idiotype response" does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention "was ready for patenting" such as by the use of drawings or structural chemical formulas that show that the invention was complete, or

describing distinguishing identifying characteristics sufficient to show that the applicant was in Possession of the claimed invention.

The claimed invention is drawn to "molecules sufficient to induce an anti-idiotype response". However, no structural or specific functional characteristics of such molecules is provided, nor is there any indication that the artisan actually used the methods of making the molecules. This situation is analogous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention. The claim fails to comply with the written description requirement.

Claims 1, 4, 5, 7-11, 14, 15, 17-21, 22 and 25-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the

claims. Such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

The instant fact pattern fails to disclose any particular structure for the claimed "molecules sufficient to induce an anti-idiotype response". The specification does not provide any guidance or any working examples in this unpredictable art, and thus the artisan would have been unable to have prepared the claimed "molecules sufficient to induce an anti-idiotype response" without undue experimentation. Furthermore an assay for finding a product is not equivalent to a positive recitation of how to make such a product. This claim fails to meet the enablement requirement for the "how to make" prong of 35 U.S.C. § 112 first paragraph.

The composition of the instant invention is directed to "vaccine" which is intended as a contraceptive. Anti-idiotype antibodies to GnRH reproduces the same biological actions as the hormone itself does, the antibody is able to bind the GnRH hormone receptor on cells to increase the intracellular calcium [Karande et al. Antiidiotypic antibody to gonadotropin releasing hormone as probe for cell surface receptors. Biochemical and Molecular Biology International (1998) Vol. 46, No. 3, pages 449-59]. A GnRH is hormone capable of promoting gonadal growth and function; such as stimulation of follicular growth or of androgen formation; most GnRH exert their effects in both sexes, although the effect of a given GnRH will differ in males and females. Therefore, it is not clear how a molecule that will mimic the natural hormone will have the desired effect of working as a contraceptive [vaccine].

There is a high level of unpredictability in the art, the art regarding the binding ability of a monoclonal antibody (i.e. a molecule sufficient to induce an anti-idiotype response) to the gonadotrophin releasing hormone (GnRH), the binding appears to be highly dependent on the

glycosylation of the monoclonal antibody [Khurana et al. The variable domain glycosylation in a monoclonal antibody specific to GnRH modulates antigen binding. Biochemical Biophysical Research Communications (1997) Vol. 234, No. 2, pages 465-469]. The claims as written do not stipulate that the one or more amino acid substitutions of the identical molecules do not effect the glycosylation which is essential for the antigen binding and presumably will be essential for providing the mold to which the anti-idiotype antibody will bind.

Furthermore, it is not clear that by mutations in the light or heavy chain will not have a deleterious effect on the binding pocket (i.e. ability to bind original antigen) of the antibody that binds the GnRH. The art has shown a single antibody molecule in which the heavy chain has a deletion in a disulfide bridge of the variable region, the mutation in this molecule did not effect the binding of the molecule. However it is not clear that this will be the case for any and all mutations in all other antibody molecules [Rudikoff et al. Functional antibody lacking a variable-region disulfide bridge. Proceedings of the National Academy of Science U S A. (1986) Vol. 83, No. 20, pages 7875-7878, cited on IDS]. Mutating the cysteine at position 23 in the light chain leads to a loss of the binding activity of the immunoglobulin, unless the immunoglobulin is stabilized with a second mutation at the same time [Frisch et al. A soluble immunoglobulin variable domain without a disulfide bridge: construction, accumulation in the cytoplasm of E. coli, purification and physicochemical characterization. Biological Chemistry Hoppe Seyler (1994) Vol. 375, No. 5, pages 353-536; Frisch et al. Contribution of the intramolecular disulfide bridge to the folding stability of REIv, the variable domain of a human immunoglobulin kappa light chain. Folding and Design (1996) Vol. 1, No. 6, pages 431-440].

An additional interpretation of the instant claims is that the second antibody comprises an "a portion of an antigen of a cell or protein involved in reproduction function". The art has disclosed the insertion of a parasite antigen into the variable domain of an antibody, and that this engeniered antibody is able to elicit a humeral immune response to an unrelated exogenous antigen [see discussion, Billetta et al. Immunogenicity of an engineered internal image antibody. Proceedings of the National Academy of Science USA (1991) Vol. 88, pages 4713-4717, cited on IDS]. The specification has provided not examples that these particular molecules have been made. There is further uncertainty in that it is the critical epitope needed for the function as a "vaccine contraceptive" would require undue experimentation.

Any mutations that change the binding affinity of the original antibody (i.e. molecule sufficient to induce an anti-idiotype response), which serves as the mold for the anti-idiotype antibody, will affect the structure of the anti-idiotype antibody because it will not be predicable whether the anti-idiotype antibody will emulate (mirror) the original antigen. Thus, the lack of working examples, lack of guidance in the specification and the prior art, the unpredictability of the art of antibody engineering and the great breadth of the claims greatly reduces the probability that one of skill In the art would successfully obtain the claimed invention without undue experimentation. Treatment/administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the subject or patient. In the absence of additional information the skilled artisan would not have been able to use the undisclosed compound(s) for treatment without undue experimentation.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, 10, 11, 14, 15, 20, 21, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Esbenshade (U.S. Pat. No. 4,556,555).

The instant invention is drawn to a composition comprising two (or more) antibodies that are capable of inducing an anti-idiotype response. The antibodies can have an unlimited number of amino acid substitutions between the molecules (35 U.S.C. 112 second paragraph rejection above). The substituted residues being the substitution of one or more amino acid residues that do not have a sulfhydryl group.

Esbenshade disclose the production and purification of antibodies to gonadotropin-releasing hormone (see columns 2, lines 42-58). These antibodies meet the limitation of being "sufficient to induce an anti-idiotype response". The reference discloses a method of using the antibodies to induce sterilization in an animal (see claims). Therefore, the instant invention is anticipated by Esbenshade.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294, please note after February 2004 the telephone number will change to 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please use 703-746-3162, please note after February 2004 the fax phone number will change to 571-273-0912.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER
2/23/04